NFA-305-(Orket. management Br.)

Date of Approval: FEB 2 1999

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-064

PULMOTIL® 90 Type A Medicated Article

(tilmicosin phosphate)

Sponsored by:

Elanco Animal Health
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

NADA 141-064

FOIS 1

I. GENERAL INFORMATION

NADA Number: 141-064

Sponsor: Elanco Animal Health
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Established Name: tilmicosin phosphate

Proprietary Name: PULMOTIL® 90

Marketing Status: Federal (USA) law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this Veterinary Feed Directive (VFD) drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice.

Effect of Supplement:

1. The addition of the following caution statement to labeling.

   "Caution: Do not allow horses or other equine access to feeds containing tilmicosin."

2. The codification under 21 CFR 556.735, of an acceptable daily intake (ADI) in man and a muscle tolerance for parent tilmicosin in swine muscle.

II. INDICATIONS FOR USE

PULMOTIL® 90 is indicated for the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.

III. DOSAGE

A. *Dosage Form*: Type A medicated article containing tilmicosin phosphate at 90.9 g/lb (200 g/kg), to be mixed either in a Type B medicated feed or in a finished Type C medicated feed for swine. PULMOTIL® 90 is supplied in 25-lb bags.

B. *Route of Administration*: Oral, in feed.

C. *Recommended Dose Range:* PULMOTIL® 90 should be fed at a dose rate of 181 g to 363 g tilmicosin phosphate per ton of complete feed (200 to 400 ppm). Feed continuously as the sole ration for a 21-day period, beginning approximately seven (7) days before an anticipated disease outbreak.

IV. EFFECTIVENESS

As discussed in the FOI Summary for the original approval of NADA 141-064.

V. ANIMAL SAFETY

As discussed in the FOI Summary for the original approval of NADA 141-064.

The safety of PULMOTIL® 90 in the equine was evaluated in a study in which tilmicosin was included in the diet of 18 adult horses for a period of 14 days at dose levels of 400, 1200, and 2000 ppm. Some horses at both the low and high dose levels demonstrated gastrointestinal disturbance, with more severe colic evident at the higher levels. One horse died after consuming the 2000 ppm diet. Accordingly, the following caution statement has been added to labeling: Do not allow horses or other equine access to feeds containing tilmicosin.

VI. HUMAN FOOD SAFETY

A. Toxicology and residue and metabolism studies

The basic toxicology and residue chemistry studies that support the use of tilmicosin in swine are summarized in the FOI Summaries for the original approvals of tilmicosin under NADA 140-929 (toxicology data) and NADA 141-064 (residue and metabolism data). Based on the toxicology studies, an acceptable daily intake of 25 mcg/kg bw/day was calculated, and the safe concentrations for total tilmicosin residues of 5 ppm in muscle, 15 ppm in liver, 30 ppm in kidney, and 30 ppm in fat were assigned to swine. The residue and metabolism studies established 7.5 ppm as the tolerance for residues of parent tilmicosin (the marker residue) in swine liver (the target tissue).

B. Assignment of a muscle tolerance

A muscle tolerance of 0.1 ppm parent tilmicosin is assigned following a review of the residue studies conducted with tilmicosin in swine in support of the original approval of NADA 141-064. The residue and metabolism data in study T5C759201 show that unchanged tilmicosin represents greater than 50% of the total residue present in swine muscle tissue following administration of the drug in feed. Those results confirm that parent tilmicosin can serve as the marker residue in swine muscle.

The muscle tolerance value of 0.1 ppm is assigned based on the data in total residue study T5C759201 and in marker residue depletion study T5C619301. Those data show that parent tilmicosin was in the range of 0.2 to 0.4 ppm at zero withdrawal (6 to 12 hours) following treatment with tilmicosin at levels of 400 ppm in the feed. Residues of unchanged tilmicosin depleted rapidly from swine muscle and were less than the 0.02 ppm detection limit of the HPLC assay used in the residue study at 7 days of withdrawal. The choice of 0.1 ppm as the tolerance for tilmicosin in swine muscle makes it possible to identify animals that have been treated with the drug and slaughtered 2 to 3 days post-treatment.

VII. AGENCY CONCLUSIONS

The minor label revision submitted in support of this supplemental NADA complies with the requirements of Section 512 of the Food, Drug, and Cosmetic Act and Part 514 of the implementing regulations. In accordance with 21 CFR 514.106(b)(1)(xiv), this is a Category I supplement which did not require re-evaluation of the safety and effectiveness data of the parent application.

Based on data submitted in support of the original approval of this NADA, a tolerance of 0.1 ppm has been established with this supplement for tilmicosin in swine muscle. The acceptable daily intake (ADI) (25 micrograms per kilogram of body weight per day) and the tolerance for tilmicosin in swine muscle (0.1 ppm) will be codified under 21 CFR 556.735.

FDA has determined under 21 CFR 25.33(a)(1) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

PULMOTIL® 90 is under U.S. patent number 4,820,695 which expires April 11, 2006.

VIII. APPROVED PRODUCT LABELING

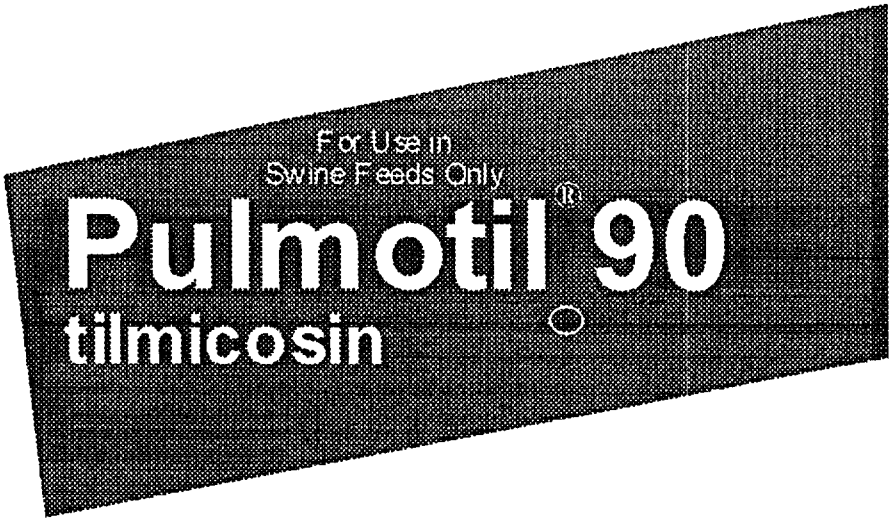
A copy of the draft facsimile labeling is attached to this document.

A. PULMOTIL® 90 Type A Medicated Article Bag Label

B. PULMOTIL® 90 Bluebird Label for Type B Medicated Feed

C. PULMOTIL® 90 Bluebird Label for Type C Medicated Feed

ELANCO AF0472-25B



Net Weight 10 Kg (22.7 lb)

Type A Medicated Article

Do not feed undiluted.

CAUTION: Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice.

Active Drug Ingredient: tilmicosin (as tilmicosin phosphate) 90.7 g per lb (200 g per kg)
Inert ingredients: ground corn cobs

Description: Pulmotil is a formulation of the antibiotic tilmicosin. Tilmicosin is produced semi-synthetically and is in the macrolide class of antibiotics. Each kilogram of Type A Medicated Article contains 200 grams (0.44 lbs) of tilmicosin adsorbed onto ground corn cobs.

Activity: Tilmicosin has an *in vitro** antibacterial spectrum that is predominately Gram-positive with activity against certain Gram-negative microorganisms. Activity against several mycoplasma species has also been detected.

Microorganism	MIC (ug/ml)
Actinobacillus pleuropneumoniae	16
Pasteurella multocida	8
Mycoplasma hyopneumoniae	0.5
Escherichia coli	>64.0
Salmonella cholerae-suis	>64.0
Streptococcus suis	>64.0

* The clinical significance of these *in vitro* data in swine has not been demonstrated.

Pharmacology: Oral dosing of tilmicosin phosphate at 181 to 363 g/ton of feed results in serum tilmicosin levels which do not correlate with efficacy. Lung concentrations of tilmicosin are significantly higher than serum. Lung levels are achieved within 2 days after beginning feeding and plateau by 4 days. Swine alveolar macrophages have been shown *in vitro* to concentrate large amounts of tilmicosin; these cells may serve as an important reservoir in lung tissue.

Indications: Pulmotil is indicated for the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida.*

CAUTION: Do not allow horses or other equine access to feeds containing tilmicosin. The safety of tilmicosin has not been established in pregnant swine or swine intended for breeding purposes.

Warning: Feeds containing Pulmotil must be withdrawn 7 days prior to slaughter.

Warning: Avoid inhalation, oral exposure, and direct contact with skin or eyes. Operators mixing and handling Pulmotil 90 should use protective clothing, impervious gloves, goggles, and a NIOSH-approved dust mask. Wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water. If irritation persists, seek medical attention. Not for human consumption. Keep out of reach of children. The Material Safety Data Sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information, or to obtain a material safety data sheet, call 1-800-428-4441.

Adverse Drug Reactions: No adverse toxicological effects were observed in swine given rations containing 2000 ppm tilmicosin for 42 days and 4000 ppm for 21 days.

Toxicology: The cardiovascular system is the target of toxicity in laboratory and domestic animals given tilmicosin by oral or parenteral routes. Primary cardiac effects are increased heart rate (tachycardia) and decreased contractility (negative inotropy). Given orally, the median lethal dose is 800 mg/kg in fasted rats and 2250 mg/kg in non-fasted rats. No compound-related lesions were found at necropsy. Results of genetic toxicology studies were all negative. Results of teratology and reproduction studies in rats were all negative. The no effect level in dogs after daily oral doses for up to one year is 4 mg/kg of body weight.

Feeding Directions: Pulmotil is to be fed continuously at 181grams to 363 grams tilmicosin per ton (200 ppm to 400 ppm) of Type C medicated feed as the sole ration for a 21-day period, beginning approximately 7 days before an anticipated disease outbreak.

IMPORTANT: Must be thoroughly mixed in feeds before use.

Mixing: Thoroughly mix Pulmotil Type A medicated article with feed to provide a Type B medicated feed containing up to 36,300 grams tilmicosin per ton or to provide a complete Type C medicated feed containing 181 to 363 g tilmicosin per ton. Do not use in concentrates or feeds containing bentonite. Bentonite in feeds may affect the efficacy of tilmicosin.

Starting concentration of Pulmotil Type A Medicated Article	Amount of Type A Medicated Article to add per ton	Resulting concentration in Type B Medicated Feed	
grams per pound	pounds	grams per ton	grams per pound
90.7	400	36,300	18.1
	300	27,200	13.6
	200	18,100	9.05

Starting concentration of Pulmotil Type A Medicated Article	Amount of Type A Medicated Article to add per ton	Resulting concentration in Type C Medicated Feed
grams per pound	pounds	grams per ton
90.7	4	363
	3	272
	2	181

For Technical Service Call:1-800-428-4441

Avoid moisture and excessive heat (40° C)

Not to be used after the date printed on the bag.

Elanco Animal Health
A Division of Eli Lilly and Company
Indianapolis, IN 46285, USA

NADA 141 - 064, Approved by FDA.

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(Lot number and expiry date are printed on the bag.)

(8/11/97)

BLUEBIRD FEED COMPANY

BLUEBIRD SWINE FEED CONCENTRATE

Type B Medicated Feed

Do Not Feed Undiluted

FOR USE IN SWINE FEEDS ONLY

Net Weight: _____ lb

CAUTION: Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice.

IMPORTANT: Must be thoroughly mixed into feeds before use.

ACTIVE DRUG INGREDIENT: tilmicosin (as tilmicosin phosphate) ...._____ grams per ton
(up to 36,300 grams per ton)

INGREDIENTS

GUARANTEED ANALYSIS

INDICATIONS: Pulmotil is indicated for the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.

MIXING : Thoroughly mix BLUEBIRD SWINE FEED CONCENTRATE with feed to provide a Type B medicated feed containing up to 36,300 grams tilmicosin per ton or to provide a complete Type C medicated feed containing 181 to 363 g tilmicosin per ton. Do not use in concentrates or feeds containing bentonite. Bentonite in feeds may affect the efficacy of tilmicosin.

Starting concentration of BLUEBIRD Type B Medicated Feed		Amount of Type B Medicated Feed to add per ton	Resulting concentration in Type B Medicated Feed	
grams per ton	grams per pound	pounds	grams per ton	grams per pound
36,300	18.1	1,500	27,200	13.6
		1,000	18,100	9.05
27,200	13.6	1,330	18,100	9.05

Starting concentration of BLUEBIRD Type B Medicated Feed		Amount of Type B Medicated Feed to add per ton	Resulting concentration in Type C Medicated Feed
grams per ton	grams per pound	pounds	grams per ton
36,300	18.1	20	363
		15	272
		10	181
27,200	13.6	26.7	363
		20	272
		13.3	181
18,100	9.05	40.1	363
		30.1	272
		20	181

FEEDING: Feed continuously as the sole ration for a 21-day period, beginning approximately seven (7) days before an expected disease outbreak.

Warning: Feeds containing Pulmotil must be withdrawn 7 days prior to slaughter.

Warning: Avoid inhalation, oral exposure, and direct contact with skin or eyes. Operators mixing and handling Pulmotil should use protective clothing, impervious gloves, goggles, and a NIOSH-approved dust mask. Wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water. If irritation persists, seek medical attention. Not for human consumption. Keep out of reach of children. The Material Safety Data Sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information, or to obtain a material safety data sheet, call 1-800-428-4441.

CAUTION: Do not allow horses or other equine access to feeds containing tilmicosin. The safety of tilmicosin has not been established in pregnant swine or swine intended for breeding purposes.

For Technical Service Call: 1-800-428-4441
Lot no. _____
Expiry date _____

Manufactured by:
Bluebird Feed Company
Robin, IL

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8/11/97

BLUEBIRD FEED COMPANY

BLUEBIRD SWINE FEED

Type C Medicated Feed

FOR USE IN SWINE ONLY

Net Weight: _____ lb

CAUTION: Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice.

ACTIVE DRUG INGREDIENT: Tilmicosin (as tilmicosin phosphate) ...._____ g per ton
(181 to 363 g per ton)

INGREDIENTS

GUARANTEED ANALYSIS

INDICATIONS: Pulmotil is indicated for the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.

FEEDING: Feed continuously as the sole ration for a 21-day period, beginning approximately seven (7) days before an expected disease outbreak.

Warning: Feeds containing Pulmotil must be withdrawn 7 days prior to slaughter.

For Emergency Medical Information, to Report an Adverse Effect, or for Technical Service Call: 1-800-428-4441

CAUTION: Do not allow horses or other equine access to feeds containing tilmicosin. The safety of tilmicosin has not been established in pregnant swine or swine intended for breeding purposes.

Lot no. _____

Manufactured by:
Bluebird Feed Company
Robin, IL

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8/11/97